



(51) International Patent Classification:

A61K 31/506 (2006.01) *A61K 33/06* (2006.01)
A61K 45/06 (2006.01) *A61K 33/42* (2006.01)
A61K 38/29 (2006.01) *A61P 35/00* (2006.01)
A61K 31/59 (2006.01) *A61P 35/04* (2006.01)

(21) International Application Number:

PCT/IB2016/053056

(22) International Filing Date:

25 May 2016 (25.05.2016)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/167,466 28 May 2015 (28.05.2015) US

(71) Applicant (for all designated States except US): **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, 4056 Basel (CH).

(72) Inventors; and

(71) Applicants (for US only): **GRAUS PORTA, Diana** [ES/CH]; c/o Novartis Pharma AG, Postfach, Basel (CH).
ISAACS, Randi [US/US]; c/o Novartis Pharma AG, Postfach, Basel (CH).

(74) Agent: **HAN, Michelle**; NOVARTIS PHARMACEUTICALS CORPORATION, One Health Plaza, East Hanover, New Jersey 07936 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM,

AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

Published:

- with international search report (Art. 21(3))

(54) Title: FGFR INHIBITOR FOR USE IN THE TREATMENT OF THE PHOSPHATURIC MESENCHYMAL TUMOR

(57) Abstract: The present invention relates generally to 3-(2,6-Dichloro-3,5-dimethoxy-phenyl)-1-{6-[4-(4-ethyl-piperazin-1-yl)-phenylamino]-pyrimid-4-yl}-1-methyl-urea or a pharmaceutically acceptable salt or a pharmaceutical composition comprising 3-(2,6-Dichloro-3,5-dimethoxy-phenyl)-1-{6-[4-(4-ethyl-piperazin-1-yl)-phenylamino]-pyrimid-4-yl}-1-methyl-urea or a pharmaceutically acceptable salt for use in the treatment of phosphaturic mesenchymal tumors.



**EGFR INHIBITOR FOR USE IN THE TREATMENT OF THE PHOSPHATURIC
MESENCHYMAL TUMOR**

FIELD OF THE INVENTION

5 The present invention relates to 3-(2,6-Dichloro-3,5-dimethoxy-phenyl)-1-{6-[4-(4-ethyl-piperazin-1-yl)-phenylamino]-pyrimid-4-yl}-1-methyl-urea or a pharmaceutically acceptable salt or a pharmaceutical composition comprising 3-(2,6-Dichloro-3,5-dimethoxy-phenyl)-1-{6-[4-(4-ethyl-piperazin-1-yl)-phenylamino]-pyrimid-4-yl}-1-methyl-urea or a pharmaceutically acceptable salt for use in the treatment of phosphaturic mesenchymal tumors.

10 **BACKGROUND OF THE INVENTION**

Phosphaturic mesenchymal tumors (PMTs) are uncommon soft tissue and bone tumors. PMTs are a group of tumors with a spectrum of histopathologic findings that include a background of spindle / stellate cells with low nuclear and mitotic activity. Prominent vascularity is common and includes vessels of different sizes and patterns, consistent with the
15 fact that they are most commonly classified as hemangiopericytomas. Osteoclast-like giant cells are frequently seen in these tumors and mature fat or lamellar bone can be present as well. FGF23 staining is positive and appears in the cytoplasm of the tumor cells. The histopathologic diagnosis of malignant disease is difficult, as even in clinically proven metastatic disease the cellular features appear benign. PMTs are subdivided in to four
20 categories: mixed connective tissue variant (PMTMCT), osteoblastoma-like variant, non-ossifying fibroma-like variant, and ossifying fibroma-like variant.

PMTs typically cause hypophosphatemia and tumor-induced osteomalacia (TIO) through secretion of phosphatonins including FGF23. Patients, having tumor-induce osteomalacia (TIO) syndrome, present with bone pain, fractures, and muscle weakness. The
25 current treatment for PMT is typically a surgical resection. However, nonspecific symptoms of fatigue, bone pain, and musculoskeletal weakness make the diagnosis elusive and lead to a delay in surgical treatment. Furthermore, mesenchymal tumors are typically very small and difficult to locate, which further delays definitive therapy by surgery for many patients. In some cases, PMTs may have already metastasized by the time the patient is diagnosed, which

makes the treatment by surgical resection impossible. For tumors that cannot be located or surgically removed medical treatment with phosphate supplements and active vitamin D (calcitriol or alphacalcidol) are usually utilized. Since phosphorus is rapidly absorbed and cleared, multiple doses throughout the day are necessary (at least 3–4 times per day).

- 5 Unfortunately, oral phosphate supplementation is poorly tolerated, and often causes upset GI and diarrhea. Hence, there is a need for a reliable and efficacious medication for the treatment of PMTs.

SUMMARY OF THE INVENTION

- 10 It is an object of the present invention to provide a medicament for the treatment of the phosphaturic mesenchymal tumors, and particularly wherein said tumor harbors FGFR alteration, furthermore for FGFR alteration with FN1-FGFR1 fusion gene.

- 15 In accordance with the present invention, it has been found that FGFR inhibitor 3-(2,6-Dichloro-3,5-dimethoxy-phenyl)-1-{6-[4-(4-ethyl-piperazin-1-yl)-phenylamino]-pyrimid-4-yl}-1-methyl-urea or a pharmaceutically acceptable salt has a beneficial dual activity, anti-cancer activity as well as treating metabolic syndrome tumor-induced osteomalacia (TIO), in the treatment of phosphaturic mesenchymal tumors, particularly wherein said tumor is associated with tumor-induced osteomalacia, and particularly wherein said tumor harbors FGFR alteration.

- 20 In another aspect, the present invention relates to the compound 3-(2,6-Dichloro-3,5-dimethoxy-phenyl)-1-{6-[4-(4-ethyl-piperazin-1-yl)-phenylamino]-pyrimid-4-yl}-1-methyl-urea or a pharmaceutically acceptable salt for use in the treatment of phosphaturic mesenchymal tumor, wherein said tumor is metastatic tumor and / or wherein said tumor is unresectable and / or cannot be located.

- 25 In another aspect, the present invention relates to the compound 3-(2,6-Dichloro-3,5-dimethoxy-phenyl)-1-{6-[4-(4-ethyl-piperazin-1-yl)-phenylamino]-pyrimid-4-yl}-1-methyl-urea or a pharmaceutically acceptable salt for use in the treatment of phosphaturic mesenchymal tumor, wherein said tumor harbors FGFR alteration, particularly FGFR1 alteration, more particularly FGFR1 gene translocation, more particularly FN1-FGFR1 gene fusion.

In another aspect, the present invention relates to the compound 3-(2,6-Dichloro-3,5-dimethoxy-phenyl)-1-{6-[4-(4-ethyl-piperazin-1-yl)-phenylamino]-pyrimid-4-yl}-1-methyl-urea or a pharmaceutically acceptable salt for use in the treatment of phosphaturic mesenchymal tumors in combination with phosphate, calcium, osteopontin (OPN),
5 parathyroid hormone or its analogue (PTH), and / or vitamin D or vitamin D analogue, preferably in combination with phosphate, calcium and / or vitamin D or vitamin D analogue, particularly vitamin D or vitamin D analogue.

In a further aspect, the present invention relates to a pharmaceutical composition comprising 3-(2,6-Dichloro-3,5-dimethoxy-phenyl)-1-{6-[4-(4-ethyl-piperazin-1-yl)-
0 phenylamino]-pyrimid-4-yl}-1-methyl-urea or a pharmaceutically acceptable salt for use in the treatment of phosphaturic mesenchymal tumors, and particularly wherein said tumor harbors FGFR alteration.

In another aspect, the invention provides a method for treating a patient having a phosphaturic mesenchymal tumor, comprising administering to said patient therapeutically
5 effective amount of 3-(2,6-Dichloro-3,5-dimethoxy-phenyl)-1-{6-[4-(4-ethyl-piperazin-1-yl)-phenylamino]-pyrimid-4-yl}-1-methyl-urea or a pharmaceutically acceptable salt.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 FDG-PET CT performed before the onset of COMPOUND A treatment (27th January
0 2015) and after the first cycle of COMPOUND A treatment was completed (1st May 2015).

FIG. 2 FDG PET scans performed before the 1st, 2nd and 3rd cycles of treatment with COMPOUND A of one patient. Treatment resulted in disappearance of pulmonary and hepatic metastases after just one cycle, and progressive shrinkage of multiple metastatic lesions (arrows).

5 **FIG. 3** Serum phosphate levels of the same patient as in FIG. 2 before, during and after the 1st, 2nd and 3rd cycles of treatment with COMPOUND A. Serum phosphate increased during treatment and returned to baseline off level.

FIG. 4 Plasma FGF23 levels of the same patient as in FIG. 2 during the 1st, 2nd and 3rd cycles of treatment with COMPOUND A. Plasma FGF23 levels, which were approximately 100 fold above normal before treatment, decreased to normal on drug and increased off. Off-drug FGF23 values progressively decreased with each cycle.

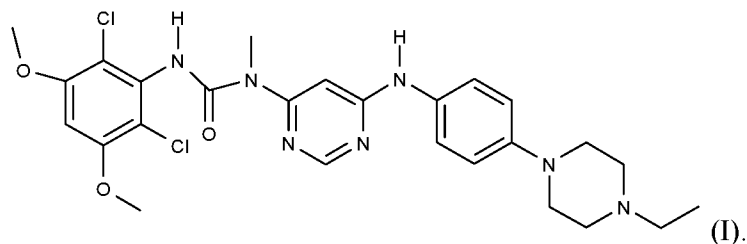
5

DETAILED DESCRIPTION OF THE INVENTION

The fibroblast growth factor 23 (FGF23) is considered a member of the fibroblast growth factor family with broad biological activities. The sequence of the protein and / or the coding sequence of the protein can be retrieved from publicly available databases known in the art. Human FGF23 is also known in the art as ADHR; HYPF; HPDR2; PHPTC. FGF23 is the disease-causing factor in several hypophosphatemic conditions. Unexpectedly it was observed that pharmacological inhibition of FGFRs using the FGFR inhibitor 3-(2,6-Dichloro-3,5-dimethoxy-phenyl)-1-{6-[4-(4-ethyl-piperazin-1-yl)-phenylamino]-pyrimid-4-yl}-1-methyl-urea (COMPOUND A) has a beneficial dual activity (anti-cancer activity as well as treating metabolic syndrome tumor-induced osteomalacia (TIO)) in the treatment of phosphaturic mesenchymal tumors.

It was found that 3-(2,6-Dichloro-3,5-dimethoxy-phenyl)-1-{6-[4-(4-ethyl-piperazin-1-yl)-phenylamino]-pyrimid-4-yl}-1-methyl-urea or a pharmaceutically acceptable salt can be very efficacious when used in the treatment of phosphaturic mesenchymal tumors. Furthermore it was found that 3-(2,6-Dichloro-3,5-dimethoxy-phenyl)-1-{6-[4-(4-ethyl-piperazin-1-yl)-phenylamino]-pyrimid-4-yl}-1-methyl-urea or a pharmaceutically acceptable salt can be very efficacious when used in the treatment of tumor-induced osteomalacia (TIO).

FGFR inhibitor 3-(2,6-Dichloro-3,5-dimethoxy-phenyl)-1-{6-[4-(4-ethyl-piperazin-1-yl)-phenylamino]-pyrimid-4-yl}-1-methyl-urea (COMPOUND A) is a compound of formula I:



The preparation of COMPOUND A described in Example 145 of WO2006/000420.

The term “pharmaceutically acceptable salts” refers to salts that retain the biological effectiveness and properties of the compound when used according to this invention and, which typically are not biologically or otherwise undesirable. Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids, e.g., acetate, aspartate, benzoate, besylate, bromide / hydrobromide, bicarbonate / carbonate, bisulfate/sulfate, camphorsulfonate, chloride/hydrochloride, chlortheophyllonate, citrate, ethandisulfonate, fumarate, gluceptate, gluconate, glucuronate, oleate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, propionate, stearate, succinate, sulfosalicylate, tartrate, tosylate, trifluoroacetate salt or the like. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like.

In one embodiment, the pharmaceutically acceptable salt is monophosphoric acid salt (or phosphate) of the compound 3-(2,6-Dichloro-3,5-dimethoxy-phenyl)-1-{6-[4-(4-ethyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-yl}-1-methyl-urea, which can optionally be in anhydrous crystalline form. In specific embodiment, the salt of the compound is any salt or form disclosed in WO2011/071821.

In one embodiment, 3-(2,6-Dichloro-3,5-dimethoxy-phenyl)-1-{6-[4-(4-ethyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-yl}-1-methyl-urea is in its free base form.

As used herein, the term “treat”, “treating” or “treatment” of any disease or disorder refers in one embodiment, to ameliorating the disease or disorder (i.e., slowing or arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another embodiment “treat”, “treating” or “treatment” refers to alleviating or ameliorating at

least one physical parameter including those that may not be discernible by the patient. In yet another embodiment, “treat”, “treating” or “treatment” refers to modulating the disease or disorder, either physically, (e.g., stabilization of a discernible symptom), physiologically, (e.g., stabilization of a physical parameter), or both. In yet another embodiment, “treat”, “treating” or “treatment” refers to preventing or delaying the onset or development or progression of the disease or disorder.

The efficacy of COMPOUND A or a pharmaceutically acceptable salt in the treatment of phosphaturic mesenchymal tumors is the normalization of FGF23. In another aspect, the efficacy of COMPOUND A or a pharmaceutically acceptable salt in the treatment of phosphaturic mesenchymal tumors is the normalization of serum phosphate value. Preferably, the efficacy is the normalization of serum phosphate value without the requirement for phosphate replacement while patient is in the dosing period (daily treatment of COMPOUND A). Preferably, the efficacy is the normalization of serum phosphate value without the requirement for phosphate replacement. Normal value ranges of FGF23 and serum phosphate are defined by the individual laboratories performing the tests. The term “normalized level” is a level in healthy individuals, i.e. the normal adult range. As used herein the normal adult range of serum phosphorus is 2.6-4.5 mg/dl, the normal adult range of serum FGF23 (C-terminal) is less or equal to 180 RU/ml (reference units per milliliter). The assays used for the detection of serum FGF23 and serum phosphorus are well known in the art and widely available.

Hypophosphatemia, according to the severity, is categorized and treated with different degree of phosphate replacement.

- Severe hypophosphatemia (< 1.0 mg/dL [0.3 mmol/L]) in critically ill, intubated patients or in those with clinical sequelae of hypophosphatemia (eg, hemolysis) should be managed with intravenous replacement therapy (0.08–0.16 mmol/kg) over 2-6 hours;
- Moderate hypophosphatemia (1.0–2.5 mg/dL [0.3–0.8 mmol/L]) in patients on a ventilator should be managed with intravenous replacement therapy (0.08–0.16 mmol/kg) over 2-6 hours;

- Moderate hypophosphatemia (1.0–2.5 mg/dL [0.3–0.8 mmol/L]) in nonventilated patients should be managed with oral replacement therapy (1000 mg/d);
- Mild hypophosphatemia should be managed with oral replacement therapy (1000 mg/d).

5 The term “normalization of serum phosphate value”, as used herein, is understood that patient’s serum phosphate level is restored to at least 1.8 mg/dL, at least 2.0 mg/dL, or preferably at least 2.5 mg/dL while the patient is within the dosing schedule cycle, including the resting period. Alternatively the term “normalization of serum phosphate value” is understood that patient’s serum phosphate level is restored to at least 1.8 mg/dL, at least 2.0
10 mg/dL, or preferably at least 2.5 mg/dL while the patient is in the dosing period (daily treatment of COMPOUND A), not including the resting period.

 The term “normalization of FGF23”, as used herein, is understood that the serum FGF23 level (C-terminal) of said patient is reduced, compared to self-reference level, by at least 10 fold, by at least 15 fold while the patient is within the dosing schedule cycle,
15 including the resting period, preferably even after COMPOUND A treatment is terminated for at least 3 months. Alternatively the term “normalization of FGF23”, as used herein, is understood that the serum FGF23 level (C-terminal) of said patient is reduced to the level below 3000 RU/ml (reference units per milliliter), below 2000 RU/ml, below 1000 RU/ml, below 500 RU/ml, below 180 RU/ml while the patient is within the dosing schedule cycle,
20 including the resting period, preferably even after COMPOUND A treatment is terminated for at least 3 months.

 The term “subject” or “patient” as used herein refers to a human e.g., a human suffering from a cancer, preferably phosphaturic mesenchymal tumor.

 As used herein, the term “phosphaturic mesenchymal tumor (PMT)” refers to a tumor
25 of bone or soft tissue. PMT contains neoplastic cells that are spindle to stellate in shape, normochromatic with small nuclei and indistinct nucleoli. The cells are typically embedded within a myxoid or myxochondroid matrix with calcification that can resemble chondroid or osteoid. Numerous osteoclast-like giant cells are a frequent finding, and mature fat and even lamellar bone may also be seen. A prominent feature of PMTs is an elaborate intrinsic

microvasculature with an admixture of vessel size and vascular pattern. The most common diagnosis for these tumors has been hemangiopericytoma, but it has also included hemangioma, sarcomas, ossifying fibromas, granulomas, giant cell tumors, and osteoblastomas. Four categories of PMT are distinguished: mixed connective tissue variant (PMTMCT), osteoblastoma-like variant, non-ossifying fibroma-like variant, and ossifying fibroma-like variant. PMTs are associated with rickets and osteomalacia, due to the production FGF23 by the tumor cells.

As used herein, the term “osteomalacia” refers to softening of the bones caused by defective bone mineralization secondary to inadequate levels of available phosphate and calcium, or because of overactive resorption of calcium from the bone which can be caused by hyperparathyroidism (which causes hypercalcemia). Osteomalacia in children is known as rickets. As used herein, the term “tumor-induced osteomalacia”, also known as “oncogenic osteomalacia” refers to a rare paraneoplastic syndrome of abnormal phosphate and vitamin D metabolism caused by typically small endocrine tumors that secrete FGF23. Biochemical hallmarks of the disorder are hypophosphatemia due to renal phosphate wasting, inappropriately normal or low 1,25-dihydroxy vitamin D, and elevated or inappropriately normal plasma FGF23.

In one embodiment, the present invention relates to the compound 3-(2,6-Dichloro-3,5-dimethoxy-phenyl)-1-{6-[4-(4-ethyl-piperazin-1-yl)-phenylamino]-pyrimid-4-yl}-1-methyl-urea or a pharmaceutically acceptable salt for use in treatment of phosphaturic mesenchymal tumor associated with tumor-induced osteomalacia.

The present invention also relates to the use of COMPOUND A in the treatment of phosphaturic mesenchymal tumor, wherein said tumor is characterized by FGFR signaling alteration, for example due to FGFR ligand mutation, or FGFR ligand amplification, or FGFR ligand overproduction (for example, FGF23 overproduction), or FGFR gene amplification, or FGFR deregulation, or FGFR mutation. In one embodiment, the present invention relates to the compound 3-(2,6-Dichloro-3,5-dimethoxy-phenyl)-1-{6-[4-(4-ethyl-piperazin-1-yl)-phenylamino]-pyrimid-4-yl}-1-methyl-urea or a pharmaceutically acceptable salt for use in treatment of phosphaturic mesenchymal tumor, wherein said tumor harbors FGFR alteration. FGFR alterations include FGFR gene amplification; and / or FGFR deregulation, FGFR

mutation. In a further embodiment, the present invention relates to the compound 3-(2,6-Dichloro-3,5-dimethoxy-phenyl)-1-{6-[4-(4-ethyl-piperazin-1-yl)-phenylamino]-pyrimid-4-yl}-1-methyl-urea or a pharmaceutically acceptable salt for use in treatment of phosphaturic mesenchymal tumor, wherein said tumor harbors FGFR1 gene alteration, preferably FGFR1 gene translocation.

As used herein, the term “gene translocation” refers to a chromosomal translocation caused by rearrangement of parts between nonhomologous chromosomes and wherein the translocation joins two otherwise-separated genes. In a preferred embodiment, said phosphaturic mesenchymal tumor is characterized by FGFR1 gene translocation leading to the formation of a FN1-FGFR1 gene fusion. (Lee et al., J Pathol. 2015; 235(4): 539-45).

The current treatment for PMT is typically a surgical resection. In one embodiment, the present invention relates to the compound 3-(2,6-Dichloro-3,5-dimethoxy-phenyl)-1-{6-[4-(4-ethyl-piperazin-1-yl)-phenylamino]-pyrimid-4-yl}-1-methyl-urea or a pharmaceutically acceptable salt for use in treatment of phosphaturic mesenchymal tumor in combination with surgical tumor resection. In one embodiment, administration of the compound 3-(2,6-Dichloro-3,5-dimethoxy-phenyl)-1-{6-[4-(4-ethyl-piperazin-1-yl)-phenylamino]-pyrimid-4-yl}-1-methyl-urea or a pharmaceutically acceptable salt occurs before a surgical tumor resection. In another embodiment, administration of the compound 3-(2,6-Dichloro-3,5-dimethoxy-phenyl)-1-{6-[4-(4-ethyl-piperazin-1-yl)-phenylamino]-pyrimid-4-yl}-1-methyl-urea or a pharmaceutically acceptable salt occurs after a surgical tumor resection.

In some cases, a surgical resection of PMTs is not possible. For example, in some groups of patients the tumor is never found / located, as tumors can arise in bone and soft tissue, occur from head to toe, and are typically very small in size. Also, in some cases, by the time the patient is diagnosed with PMT, the tumor may have already metastasized, which makes the tumor unresectable, and thus the treatment by surgical resection impossible. In one embodiment, the present invention relates to the compound 3-(2,6-Dichloro-3,5-dimethoxy-phenyl)-1-{6-[4-(4-ethyl-piperazin-1-yl)-phenylamino]-pyrimid-4-yl}-1-methyl-urea or a pharmaceutically acceptable salt for use in treatment of phosphaturic mesenchymal tumor, wherein said tumor is unresectable and / or cannot be located. In a further embodiment, the present invention relates to the compound 3-(2,6-Dichloro-3,5-dimethoxy-phenyl)-1-{6-[4-(4-

ethyl-piperazin-1-yl)-phenylamino]-pyrimid-4-yl}-1-methyl-urea or a pharmaceutically acceptable salt for use in treatment of metastatic phosphaturic mesenchymal tumor.

In one embodiment, the present invention relates to the compound 3-(2,6-Dichloro-3,5-dimethoxy-phenyl)-1-{6-[4-(4-ethyl-piperazin-1-yl)-phenylamino]-pyrimid-4-yl}-1-methyl-urea or a pharmaceutically acceptable salt for use in treatment of phosphaturic mesenchymal tumor, wherein the daily dose is 1-150 mg, preferably 1-100 mg, preferably 1-75 mg, more preferably 1-50 mg, more preferably 1-25 mg in weight of the compound in free base form. In one embodiment the daily dose does not change throughout the entire treatment.

In one embodiment, COMPOUND A is dosed daily without a periodic resting period.

10 In an alternative embodiment, the dosing regimen of COMPOUND A comprises administering COMPOUND A, followed by a resting period. As used herein, the term “resting period” refers, in particular, to a period of time during which the patient is not given COMPOUND A (i.e. a period of time wherein the treatment with COMPOUND A is withheld). For example, if COMPOUND A is given on a daily basis, there would be rest

15 period if the daily administration is discontinued for some time, e.g., for some number of days, or the plasma concentration of COMPOUND A is maintained at sub-therapeutic level for some time e.g., for some number of days. The dosing period and/or the dose of COMPOUND A can be the same or different between cycles. The term “treatment cycle”, as used herein, refers to a course of treatment that is repeated on a regular schedule with periods

20 of rest in between. For example, treatment given for 21 days followed by 7 days of rest is one treatment cycle. The total treatment time (i.e. the number of cycles for treatment) may also vary from patient to patient based, for example, on the particular patient being treated or the severity of the condition. In general, the treatment is administered until a satisfactory response is obtained (e.g. by administering cycles until reaching, for example, normalized FGF23

25 and/or serum phosphate values off COMPOUND A, preferably without the requirement for phosphate replacement).

The term “intermittent dose”, as used herein, refers to a dose administered in a subsequent treatment cycle to the starting dose. The earliest (first) intermittent dose is the earliest (first) dose that is different from the starting dose. Preferably, an intermittent dose is

30 maintained during the entire treatment cycle. In the next treatment cycle, the intermittent dose

can be the same or different (higher or lower) from the intermittent dose of the previous treatment cycle.

In one embodiment, an intermittent dosing schedule comprises at least two cycles, each cycle comprising (a) a dosing period during which a therapeutically effective amount of COMPOUND A is administered to said patient and thereafter (b) a resting period. In one embodiment, the dosing period is of at least one day and the resting period is of at least one day. In one embodiment, COMPOUND A, as defined herein is not given after the second rest period, i.e., when the method of the invention involves, for example, two cycles, COMPOUND A need not be administered following the second rest cycle. The term “intermittent dosing regimen of COMPOUND A”, as used herein, refers to both a dosing regimen for administering COMPOUND A alone (i.e. monotherapy) or a dosing regimen for administering COMPOUND A in combination with at least a further active agent (i.e. combination therapy).

In one embodiment, the treatment consists of a starting dose and at least one intermittent dose. In one embodiment, the starting dose is 125 mg, 100mg, 75 mg, 50 mg or 25 mg and the intermittent dose is 125 mg, 100mg, 75 mg, 50 mg or 25 mg in weight of the compound in free base form.

In one embodiment, the treatment consists of a starting dose and at least one intermittent dose, wherein said intermittent dose is less than said starting dose. In one embodiment, starting dose is 125 mg and said intermittent dose is 100 mg, preferably 75 mg. In one embodiment, starting dose is 125 mg and said intermittent dose is 75 mg. In another embodiment, the starting dose is 100 mg and said intermittent dose is 75 mg, preferably 50 mg. In another embodiment, the starting dose is 75 mg, and said intermittent dose is 50 mg, preferably 25 mg.

In one embodiment, the treatment consists of a starting dose and at least one intermittent dose, wherein said intermittent dose is more than said starting dose. In one embodiment, the starting dose is 50 mg and the intermittent dose is 100 mg, preferably 75 mg. In another embodiment, the starting dose is 75 mg and the intermittent dose is 125 mg, preferably 100 mg. In a further embodiment, the starting dose is 25 mg and the intermittent dose is 100 mg,

preferably 75, preferably 50 mg. In a further embodiment, the starting dose is 25 mg and said intermittent dose is 75 mg, preferably 50 mg.

In a further embodiment, the starting dose is administered to patient for at least one, at least two, at least three, at least four or at least five treatment cycles. In a further embodiment, the intermittent dose is administered to patient for at least one, at least two, at least three, at least four or at least five treatment cycles.

Determination of amount of treatment cycles with the starting dose and with the intermittent dose, the selection and adjustment of the starting and intermittent doses are performed based on the measurements of the levels of serum phosphorus, serum calcium and serum FGF23 levels in the patient before and after administration of COMPOUND A and their comparison to their normal adult ranges. In addition, determination of amount of treatment cycles with the starting dose and with the intermittent dose, the selection and adjustment of the starting and intermittent doses are performed based on the findings from radiological procedures, such as CT scan or FDG-PET, in the patient before and after administration of COMPOUND A and their comparison to each other.

As used herein, the term "treatment cycle" refers to a COMPOUND A treatment cycle. In one embodiment, the treatment cycle is COMPOUND A to be administered for the first 21 days of every 28 day cycle. In one embodiment of the present invention the starting dose of COMPOUND A is 125 mg, the first intermittent dose is 100 mg, and the second intermittent dose is 75 mg, wherein the starting, the first and the second intermittent doses are administered for one cycle each, wherein the treatment cycle is COMPOUND A to be administered for the first 21 days of every 28 day cycle.

A method for determining a suitable dose of COMPOUND A for the treatment of the phosphaturic mesenchymal tumor and the duration of the treatment comprising the steps of

- a) providing a sample of a subject to whom a starting dose of COMPOUND A inhibitor was administered;

- b) determining the serum level of FGF23 or the serum level of phosphorus (P), or the serum level of calcium of said sample; preferably determining the serum level of FGF23 or

the serum level of phosphorus (P); or preferably determining the serum level of phosphorus (P);

c) comparing said level of FGF23 or the serum level of phosphorus (P), or the serum level of calcium to a self-reference level or to a normal reference level; and

5 (d) adjust the starting dose to the intermittent level accordingly.

As used herein, the term "self reference level" is the level of serum FGF23, serum level of phosphorus (P), and serum level of calcium in the subject before the onset of treatment, i.e. by determining the baseline level of the subject. The term "normal reference level" is a level in healthy individuals, i.e. the normal adult range. As used herein, the normal adult range of
10 serum calcium is 8.5-10.5 mg/dl and ion calcium is 4.6-5.2 mg/dl, the normal adult range of serum phosphorus is 2.6-4.5 mg/dl, the normal adult range of serum 1,25-dihydroxy vitamin D is 18-64 pg/ml, the normal adult range of serum FGF23 (C-terminal) is less or equal to 180 RU/ml (reference units per milliliter). The assays used for the detection of serum FGF23, serum calcium and serum phosphorus are well-known in the art and widely available.

15

Methods for determining serum levels of FGF23, phosphorus and calcium are known in the field and are particularly described below. Serum FGF23 levels can be measured using the human C-terminal ELISA Kit (Immutopics Inc., San Clemente, CA, USA). The term "phosphorus level" is known in the field and in particular refers to the blood level of inorganic
20 phosphorus and may e.g. be measured in serum by ultraviolet method using kits for example from RANDOX Laboratories LTD, UK, and a clinical chemistry analyzer such as the HITACHI 717 analyzer (Roche Diagnostics). The term "calcium level" is known in the field and in particular refers to the blood level of total calcium and may e.g. be measured in serum by ultraviolet method using kits for example from RANDOX Laboratories LTD and a clinical
25 chemistry analyzer such as the HITACHI 717 analyzer.

The present invention provides an ex vivo method for determining the suitable dose of COMPOUND A for the treatment of the phosphaturic mesenchymal tumor, for adjusting the starting dose to intermittent dose, and for the duration of the treatment comprises the steps of

a) providing a sample of a subject to whom a starting dose of COMPOUND A inhibitor was administered;

b) determining the serum level of FGF23 or the serum level of phosphorus (P), or the serum level of calcium of said sample; preferably determining the serum level of FGF23 or
5 the serum level of phosphorus (P); or preferably determining the serum level of phosphorus (P);

c) comparing said level of FGF23 or the serum level of phosphorus (P), or the serum level of calcium to a self-reference level or to a normal reference level; and

(d) adjusting the starting dose to the intermittent level accordingly,

10 wherein the decrease in serum FGF23 level, and increase in serum phosphorus and serum calcium levels in comparison to the self-reference level or the normal reference level. For example, the starting dose is decreased to intermittent dose, or intermittent dose is further decreased to another intermittent dose.

The present invention provides an ex vivo method for determining the suitable dose of
15 COMPOUND A for the treatment of the phosphaturic mesenchymal tumor, for adjusting the starting dose to intermittent dose, and for the duration of the treatment comprises the steps of

a) providing a sample of a subject to whom a starting dose of COMPOUND A inhibitor was administered;

b) determining the serum level of FGF23 or the serum level of phosphorus (P), or the
20 serum level of calcium of said sample; preferably determining the serum level of FGF23 or the serum level of phosphorus (P); or preferably determining the serum level of phosphorus (P);

c) comparing said level of FGF23 or the serum level of phosphorus (P), or the serum level of calcium to a self-reference level or to a normal reference level; and

25 (d) adjusting the starting dose to the intermittent level accordingly,

wherein the increase in serum FGF23 level, and decrease in serum phosphorus and serum calcium levels in comparison to a reference level, wherein the reference level is a baseline level of the patient before the onset of the treatment, and / or wherein the serum levels of FGF23, calcium and / or phosphorus are outside of the normal adult ranges indicates that the dose should be increased. For example, the starting dose is increased to intermittent dose, or intermittent dose is further increased to a higher intermittent dose.

In one embodiment, the present invention relates to the compound 3-(2,6-Dichloro-3,5-dimethoxy-phenyl)-1-{6-[4-(4-ethyl-piperazin-1-yl)-phenylamino]-pyrimid-4-yl}-1-methyl-urea or a pharmaceutically acceptable salt for use in treatment of phosphaturic mesenchymal tumor, preferably associated with tumor-induced osteomalacia, in combination with phosphate, calcium, osteopontin (OPN), parathyroid hormone or its analogue (PTH), and / or vitamin D or vitamin D analogue, preferably in combination with phosphate, calcium and / or vitamin D or vitamin D analogue, particularly vitamin D or vitamin D analogue.

In another aspect, the present invention relates to a pharmaceutical composition comprising 3-(2,6-Dichloro-3,5-dimethoxy-phenyl)-1-{6-[4-(4-ethyl-piperazin-1-yl)-phenylamino]-pyrimid-4-yl}-1-methyl-urea or a pharmaceutically acceptable salt for use in treatment of phosphaturic mesenchymal tumor.

In a further aspect, the present invention relates to a method of treating a patient having a phosphaturic mesenchymal tumor, comprising administering to said patient therapeutically effective amount of 3-(2,6-Dichloro-3,5-dimethoxy-phenyl)-1-{6-[4-(4-ethyl-piperazin-1-yl)-phenylamino]-pyrimid-4-yl}-1-methyl-urea or a pharmaceutically acceptable salt. In one embodiment, the present invention relates to a method of treating a patient having a phosphaturic mesenchymal tumor, comprising administering to said patient therapeutically effective amount of 3-(2,6-Dichloro-3,5-dimethoxy-phenyl)-1-{6-[4-(4-ethyl-piperazin-1-yl)-phenylamino]-pyrimid-4-yl}-1-methyl-urea or a pharmaceutically acceptable salt, wherein the administration of the compound occurs before and / or after a surgical tumor resection. In a further embodiment, the present invention relates to a method of treating a patient having a phosphaturic mesenchymal tumor, comprising administering to said patient therapeutically effective amount of 3-(2,6-Dichloro-3,5-dimethoxy-phenyl)-1-{6-[4-(4-ethyl-piperazin-1-yl)-

phenylamino]-pyrimid-4-yl}-1-methyl-urea or a pharmaceutically acceptable salt, wherein said tumor is associated with tumor-induced osteomalacia.

5 The following Examples illustrates the invention described above, but is not, however, intended to limit the scope of the invention in any way. Other test models known as such to the person skilled in the pertinent art can also determine the beneficial effects of the claimed invention.

Examples

10 Example 1:

The subject of this study is a 62-year old patient, male, clinically diagnosed with recurrent hypophosphatemic osteomalacia (TIO) due to autocrine production of FGF23 from metastatic tumor (ameloblastic fibrosarcoma). Patient was diagnosed with phosphaturic mesenchymal tumor of the mandible 23 years earlier.

15 Patient's disease history (Bergwitz, C., et al., NEJM, Oct 2011, 365:1625-35):

This is a 62 year-old male with a history of tumor induced osteomalacia. The patient was first diagnosed in 1990 when he started having symptoms of rib pain, and when a left metatarsal stress fracture occurred while he was running. Phosphate supplements and calcitriol were administered, after which the patient's symptoms resolved. An extensive
20 search for a tumor was negative.

Five years later (1995), during a routine dental evaluation, swelling was noted in the area of the second bicuspid and the first molar on the bottom right (29 and 30, respectively, according to the universal numbering system). Radiographs reportedly showed a slight alteration in the trabecular pattern of the right mandible. Computed tomography (CT) of the
25 head revealed a destructive lesion (1.2 cm in diameter) in the right mandibular body, with marginal trabecular preservation, centered between the second premolar (i.e., the second

bicuspid) and the first molar on the right side. The mass was excised, and pathological examination of the specimen reportedly showed an atypical proliferation of mixed epithelial and mesenchymal cells, including fascicles of spindled cells and reactive fragments of trabecular bone; there was insufficient nuclear atypia or mitotic activity to warrant a diagnosis of a malignant tumor. Tumor was focally present at the surgical margin. After the excision, the serum phosphorus level returned to normal and supplementation with phosphate and vitamin D was stopped.

Thirteen years ago, back and rib pain, stress fractures, and hypophosphatemia recurred, and phosphate supplementation was resumed. Octreotide scanning (scintigraphy using octreotide labeled with indium-111) was reportedly positive for radionuclide uptake in the right mandible, a feature consistent with persistent or recurrent tumor. During the next 12 years, multiple surgical procedures were performed, including mandibular biopsies and resections and the insertion of a fibular implant, as well as dissection of a cervical lymph node on the right side; pathological examination of the specimens showed a spindle-cell lesion infiltrating bone and soft tissue. Hypophosphatemia and the need for treatment with phosphate and calcitriol persisted. The patient reported bilateral hip pain when walking, fatigue, muscle weakness, intermittent wheezing with exercise, and mild chronic diarrhea that was attributed to phosphate supplements. He had no fever, sweats, weight loss, chest or abdominal pain, new intestinal symptoms, or hematuria.

On examination, in 2011, there were brown, infiltrative lesions (5 to 10 mm in diameter) over the trunk and back, consistent with mastocytosis, and a mass on the back of the neck, consistent with a lipoma. The oropharynx was normal. There was enlargement of the lingual mandible anteriorly and on the right, with no dental dysplasia or dysplasia of the palate or jaw bone. There was surgical scarring and fibrosis over the mandible and neck on the right side. Panoramic occlusal radiographs of the teeth and mandible showed a radiolucency associated with the right anterior mandibular implant and a wire in the lingual cortex. The complete blood count and serum levels of electrolytes, total protein, albumin, globulin, magnesium, glucose, and tryptase were normal, as were tests of coagulation and renal and liver function. CT of the hips showed no soft-tissue calcifications and no evidence of stress fractures. Eight weeks later, samples obtained from multiple sites of venous

catheterization revealed elevated levels of fibroblast growth factor 23 (FGF23) at all sites tested, but without a clinically significant gradient in the FGF23 levels in the veins of the neck or extremities. Single-photon-emission CT (SPECT) imaging of the head, chest, and abdomen after the administration of indium-111-labeled pentetreotide revealed high uptake in the lower
5 face that was thought to be in the mandible or reconstructed bone, and subtle pentetreotide localization in the upper abdomen that was thought to be nonspecific.

Baselines upon admission to COMPOUND A treatment:

In 2015, before the onset of COMPOUND A treatment, baseline multiple metastatic lesions to lung, liver and bone were identified in the patient. Upon admission the patient
10 underwent routine blood work.

The patient was asked to hold his phosphorus, as well as cinacalcet and Calcitriol prior to admission, which he did according to the instructions. In January 2015, his phosphorus on admission was 1.1 and this was done off any phosphorus replacement. His calcium was 2.27 and ionized calcium was 1.19 with an intact parathyroid hormone level of 61.7. His 25-
15 hydroxyvitamin D level was 67 and 125 dihydroxyvitamin D level was 25. He had urine spot studies done, which showed a spot urine phosphorus level of 104 and a spot urine calcium level of 1.04. Twenty-four hour urine collections done on day 1 of admission showed a total volume of 1.28 liters with a creatinine of 1.06 g/24 hours. His urine calcium was 1.62 mmol/24 hours. Metanephrine level was 92 and normetanephrine level of 196.
20 Catecholamines showed 24 hour epinephrine level of 3.2 and norepinephrine level of 23. These were all within normal limits. Twenty-four hour 5-HIAA level was 3.8. This was also within normal limits.

The patient was restarted on his phosphorus, as well as calcitriol and cinacalcet, and his labs were repeated in February 2015, which showed a phosphorus level which had
25 improved to 2.1. His intact parathyroid hormone level was 69.8. Calcium level was 2.05. His 24-hour urine studies were repeated and his calcium was found to be 1.25 mmol/24 hours with a corresponding creatinine of 1.26 g/24 hours. Given his normal 24-hour urine calcium, as well as slightly elevated intact parathyroid hormone level his cinacalcet was increased.

The patient's FGF23 level was found to be 8850 RU/ml in January 2015.

In terms of imaging, the patient underwent bone series done in January 2015, which did not show any focal lesion suggestive of site of osteomalacia producing tumor. He had a CT scan of the chest, abdomen and pelvis, which showed increased number of pulmonary nodules, liver lesions which were concerning for neoplastic foci, indeterminate small
5 hypodensities in kidneys, extensive areas of mixed density in skeletal structure which is concerning for osteomalacia with some areas of lysis. These are present in bilateral hips, pubic symphysis. He also had nonspecific thickening of soft tissue stranding along celiac artery trunk which was a questionable hepatobiliary pathology. He also was found to have pelvic ascites in small amounts and nonspecific minimal nodular adrenal thickening. He
10 underwent an FDG-PET which showed multiple-lesions in the skeleton, lung nodules, muscles, liver, and questionable pancreatic lesion, and also lower extremity lesions. He had a DOTATATE PET scan done which showed multiple SSRT2 lesions in the skeleton, lungs, subcutaneous soft tissue, muscles, left parotid, pancreatic, mesenteric region. An octreotide scan was done which showed multiple abnormalities consistent with site of tumor, with far
15 fewer than as seen on other functional imaging. The patient had a renal ultrasound done which was normal and did not show any lesions or any hydronephrosis. This was done in order to rule out any evidence of nephrocalcinosis. The patient also underwent baseline pulmonary function testing done given his evidence of lung nodules, and this testing showed mild restrictive pattern on spirometry. The flow volume loop is suggestive of a mixed pattern. Mild
20 diffusion defect.

Phosphaturic mesenchymal tumor of the patient harbors FGFR1 genetic fusion:

FGFR1 gene translocation was found by fluorescent in situ hybridization (FISH) in patient's tumor specimen. The following methodology was used to perform FISH analysis: a dual-color, break-apart probe flanking the centromeric and telomeric sides of FGFR1 locus
25 (Cytocell, Cambridge, UK) was used to evaluate for a translocation involving FGFR1 gene. At least 100 nuclei were score, and abnormal nuclei represented 35% of scored nuclei. The percentage of nuclei with fusion signals fell within the range of threshold level $\pm 3\%$. Thus, positive FGFR1 translocation has been concluded.

Baseline before the onset of treatment with COMPOUND A of the patient:

Baseline before the onset of treatment with COMPOUND A represented multiple metastatic lesions to lung, liver and bone. Patient was receiving phosphate supplements, Calcitriol (1,25 dihydroxyvitamin D3) and cinacalcet for PO4/Ca control. While the patients FGF23 level was found to be 8850 RU/ml in January 2015, the baseline level of FGF23 before the onset of treatment was 15500 RU/ml.

Treatment with COMPOUND A of the patient:

The treatment of the patient with COMPOUND A began on 1st April 2015. COMPOUND A was administered orally as flat-fixed dose of 125 mg and not by body weight or body surface area for the first 21 days of the first 28 day cycle. During the second administration cycle, COMPOUND A was administered at a dose of 100 mg for the first 21 days of the first 28 day cycle. During the third administration cycle, COMPOUND A was administered at a dose of 75 mg for the first 21 days of the first 28 day cycle.

The laboratory assessment of cycle 1 is presented in Table 1.

In the beginning of the cycle, in addition to the COMPOUND A administration, patient was receiving phosphorus supplementation as well as calcitriol (see Table 1). Already on the third day of cycle 1, the level of FGF23 was decreased to 1765 RU/ml (see Table 1).

On day 8 of cycle 1, the patient reported “feeling great with less pain. Also, serum phosphorus level was 3.8 mg/dl, which is within normal adult range. The patient started to receive a reduced dose of Neutraphos (phosphorus supplementation was decreased to 5 times per day). The lesion on the back of the patient was softer / flatter, and reduced in size from 9x9 cm to 7x7 cm.

On day 11 of cycle 1, the patient was put off any phosphorus supplementation. Also, on day 12 of the cycle, calcitriol administration was decreased to BID. On day 12 of the cycle, the level of FGF23 was decreased to 112 RU/ml, which is within the normal adult range (less or equal to 180 RU/ml).

On day 22 of cycle 1, the patient was examined by the dentist due to mouth soreness. During this examination, the fullness of mandibular was recorded, thus the large jaw lesion

for which the patient has had multiple surgeries is no longer detectable. Furthermore, the recurrent lesion was no longer visible. The patient was taken off from all phosphorus / calcium supplement therapy, and the phosphorus level has normalized off supplementation.

During cycle 2, the dose is to be reduced to 75 mg.

- 5 On day 1 of cycle 2 (1st May 2015), FDG-PET CT was performed and showed consistent results with clinical picture and normalization of FGF23 levels (Figure 1).

Table 1. Cycle 1 laboratory assessments

Date	Cycle	Phosphorus level	Phosphorus supplementation	Calcium level	Other supplementation	FGF23 level* (RU/ml)	COMPOUND A dose
11.03.2015	Screen	1.6	Phos Neutral 250mg 6 X's/day	7.8	Calcitriol 0.25mcg BID		
30.03.2015		2.0	Phos Neutral 8 X's /day	8.3	Calcitriol 0.25mcg TID		
1.04.2015	Day 1	2.2	Kphos 15mmol IV	9.0		15500	125 mg
2.04.2015	Day 2	3.9	2 additional doses of oral phos				125 mg
3.04.2015	Day 3	2.3		8.8		1765	125 mg
6.04.2015	Day 6	3.1		9.5			125 mg
8.04.2015	Day 8	3.8	Decrease phos to 5 X's/day	9.4			125 mg
10.04.2015	Day 10	6.4		8.5			125 mg
15.04.2015	Day 15	4.1	Discontinued phos on 11.04.2015	8.5	Calcitriol decreased to BID on 4/12	112	125 mg
22.04.2015	Day 22	4.5	none	10.1		Awaiting results	125

*FGF23 level reflects the level of intact FGF23 (iFGF23).

Example 2

Tumor-induced osteomalacia (TIO) is a paraneoplastic syndrome characterized by bone pain, muscle weakness, and fractures. Symptoms are due to renal phosphate wasting, which results in hypophosphatemia and osteomalacia. TIO is caused by ectopic production of the phosphate- and vitamin D-regulating hormone, FGF23, usually by mixed tissue mesenchymal tumors. Several lines of evidence suggest a role for FGFR signaling in FGF23 regulation and TIO tumorigenesis, especially the recent finding of a fibronectin 1 (FN1)/FGFR1 gene fusion in TIO tumors that presumably generates a FN/FGFR chimeric protein with active FGFR signaling. COMPOUND A (3-(2,6-Dichloro-3,5-dimethoxy-phenyl)-1-{6-[4-(4-ethyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-yl}-1-methyl-urea) is a selective pan-FGFR inhibitor that has been shown to have anti-tumor activity in FGFR-driven tumors, and to inhibit the phosphaturic effects of FGF23 in preclinical models. These combined properties suggest a possible role for COMPOUND A in treating TIO.

We identified a FGFR rearrangement in a tumor from a patient with an extremely rare case of widely metastatic TIO, who had previously failed Yttrium-90/Lutetium-177 peptide receptor radionuclide therapy. Based on the FGFR1 rearrangement, the patient enrolled in an IRB-approved phase 2 trial (COMPOUND A Signature Trial; NCT02160041). Through cycles 1, 2, and 3, (1 cycle = 3 weeks on/1 week off drug), doses were 125, 100, and 75mg/day, respectively – adjusted to maintain normal serum phosphate levels.

The major findings are represented in the figures:

Figure 2: FDG PET scans performed before the 1st, 2nd and 3rd cycles. Treatment resulted in disappearance of pulmonary and hepatic metastases after just one cycle, and progressive shrinkage of multiple metastatic lesions (arrows);

Figure 3: serum phosphate increased during treatment and returned to baseline off;

Figure 4: plasma FGF23 levels (C-terminal, Immutopics, San Clemente, CA), which were approximately 100 fold above normal before treatment, decreased to normal on drug and increased off. Of note, off-drug FGF23 values progressively decreased with each cycle.

Treatment was accompanied by hyperuricemia. Side effects included grade 1 stomatitis, hand-foot syndrome, and retinal detachment, which were addressed by dose interruptions and reductions.

5 The data support: 1) COMPOUND A is tumoricidal to phosphaturic mesenchymal tumors in TIO, and 2) in TIO FGF23 production is FGFR-dependent. While it remains to be proven if these effects will also occur in typical non-malignant TIO, the data support a role for COMPOUND A in the treatment of TIO.

CLAIMS

1. Compound 3-(2,6-Dichloro-3,5-dimethoxy-phenyl)-1-{6-[4-(4-ethyl-piperazin-1-yl)-phenylamino]-pyrimid-4-yl}-1-methyl-urea or a pharmaceutically acceptable salt for use in the treatment of patient having phosphaturic mesenchymal tumor.
- 5 2. The compound for use according to claim 1, wherein said tumor harbors FGFR alteration.
3. The compound for use according to claim 2, wherein said FGFR alteration is FGFR1 alteration.
- 10 4. The compound for use according to claim 3, wherein said FGFR1 alteration is FN1-FGFR1 gene fusion.
5. The compound for use according to any one of the preceding claims, wherein the administration of the compound occurs before and / or after a surgical tumor resection.
- 15 6. The compound for use according to any one of the claims 1 to 4, wherein said tumor is unresectable and / or cannot be located.
7. The compound for use according to claim 5 or 6, wherein said tumor is metastatic tumor.
8. The compound for use according to anyone of the preceding claims, wherein said tumor is associated with tumor-induced osteomalacia.
- 20 9. Compound 3-(2,6-Dichloro-3,5-dimethoxy-phenyl)-1-{6-[4-(4-ethyl-piperazin-1-yl)-phenylamino]-pyrimid-4-yl}-1-methyl-urea or a pharmaceutically acceptable salt for use in the treatment of a patient having tumor-induced osteomalacia.
10. The compound for use according to any one of the claims 1 to 9 in the form of monophosphoric acid salt.

11. The compound for use according to any one of the preceding claims, wherein the daily dose is 1-150 mg, preferably 1-100 mg, preferably 1-75 mg, in weight of the compound in free base form.
12. The compound for use according to any one of the preceding claims, wherein the treatment consists of a starting dose and at least one intermittent dose.
13. The compound for use according to claim 12, wherein said intermittent dose is less than said starting dose.
14. The compound for use according to any one of claims 12 to 13, wherein said starting dose is 125 mg, 100mg, 75 mg, in weight of the compound in free base form.
15. The compound for use according to any one of claims 12 to 14, wherein said intermittent dose is 125 mg, 100mg, 75 mg, 50 mg or 25mg in weight of the compound in free base form.
16. The compound for use according to claim 13, wherein said starting dose is 125 mg and said intermittent dose is 100 mg, preferably 75 mg.
17. The compound for use according to claim 13, wherein said starting dose is 100 mg and said intermittent dose is 75 mg, preferably 50 mg.
18. The compound for use according to any one of claims 11 to 17, wherein the compound is administered according to a starting dosing schedule of cycle and an intermittent dosing schedule of at least one cycle, wherein the cycle comprising (a) a dosing period and thereafter (b) a resting period.
19. The compound for use according to any one of claims 11 to 18, wherein the compound is administered daily for the first 21 days of 28 day cycle.
20. The compound for use according to any one of claims 1 to 19 in combination with phosphate, calcium, osteopontin (OPN), parathyroid hormone or its analogue (PTH), and / or vitamin D or vitamin D analogue, preferably in combination with phosphate,

calcium and / or vitamin D or vitamin D analogue, particularly vitamin D or vitamin D analogue.

21. A pharmaceutical composition comprising 3-(2,6-Dichloro-3,5-dimethoxy-phenyl)-1-{6-[4-(4-ethyl-piperazin-1-yl)-phenylamino]-pyrimid-4-yl}-1-methyl-urea or a pharmaceutically acceptable salt for use as defined in any one of claims 1 to 20.

Figure 1

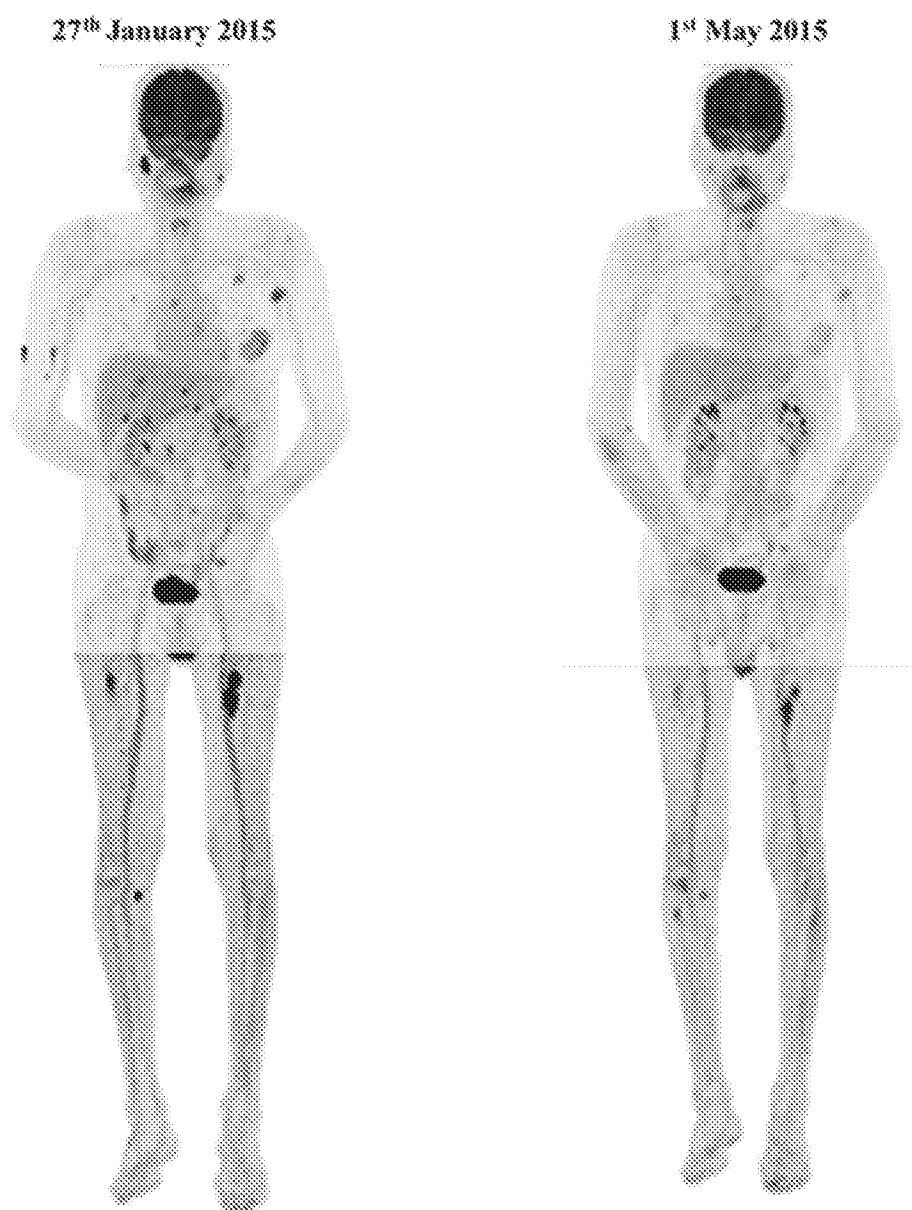


Figure 2

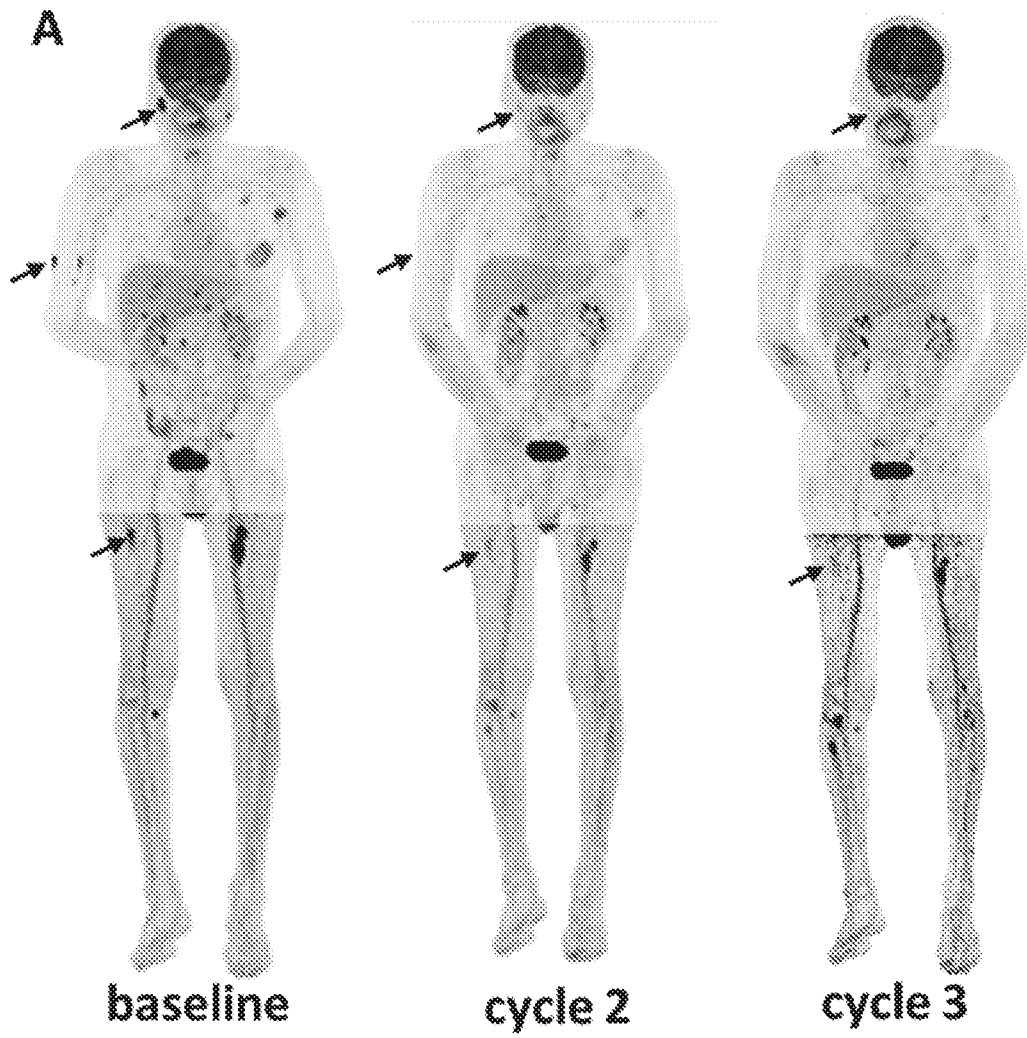


Figure 3

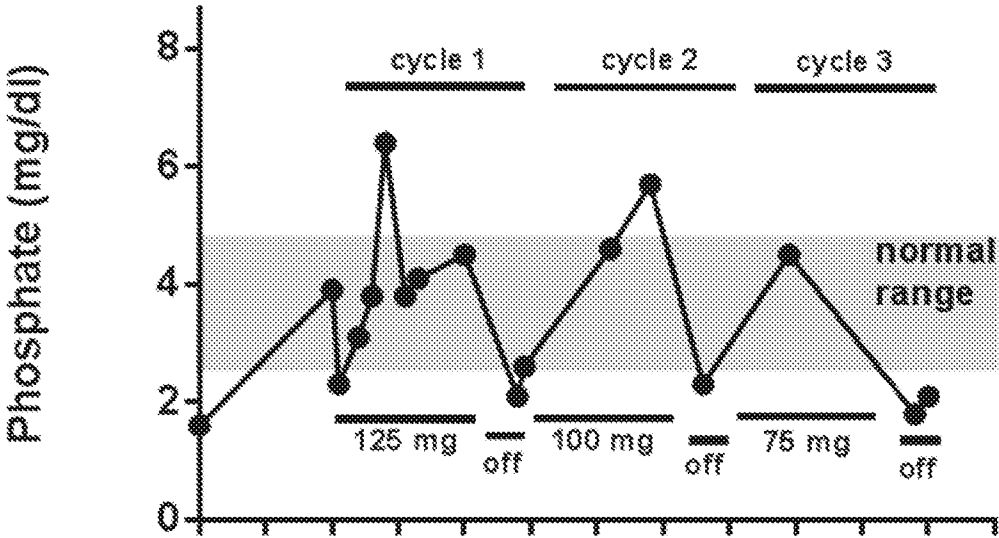
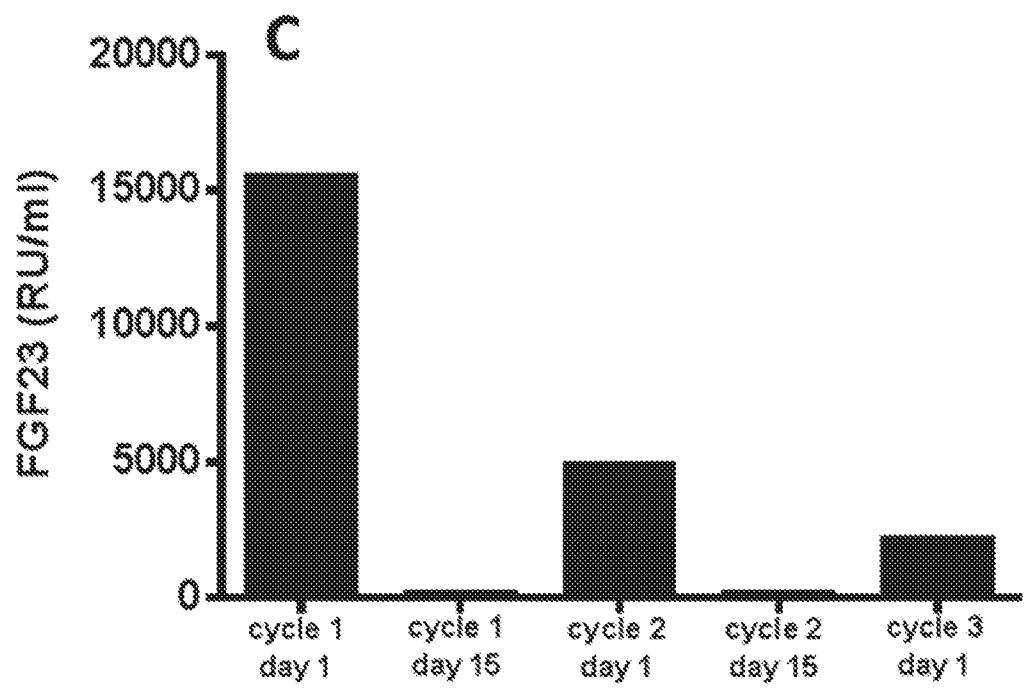


Figure 4



INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2016/053056

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/506 A61K45/06 A61K38/29 A61K31/59 A61K33/06
A61K33/42 A61P35/00 A61P35/04
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2013/144339 A1 (NOVARTIS AG [CH]; KNEISSEL MICHAELA [CH]; GUAGNANO VITO [CH]; GRAUS PO) 3 October 2013 (2013-10-03) pages 3-4, paragraph 1; claims 1, 9 page 8, paragraph 2 page 9 page 10, paragraph 4 - page 11, paragraph 1 ----- -/-	1-4, 8-11, 14-17, 20,21

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

15 July 2016

Date of mailing of the international search report

22/07/2016

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Ansaldo, M

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2016/053056

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JEN-CHIEH LEE ET AL: "Identification of a novel FN1-FGFR1 genetic fusion as a frequent event in phosphaturic mesenchymal tumour", JOURNAL OF PATHOLOGY, vol. 235, no. 4, 7 January 2015 (2015-01-07), pages 539-545, XP055288779, GB ISSN: 0022-3417, DOI: 10.1002/path.4465 abstract	1-21
X	----- V. GUAGNANO ET AL: "FGFR Genetic Alterations Predict for Sensitivity to NVP-BGJ398, a Selective Pan-FGFR Inhibitor", CANCER DISCOVERY, vol. 2, no. 12, 20 September 2012 (2012-09-20), pages 1118-1133, XP055141813, ISSN: 2159-8274, DOI: 10.1158/2159-8290.CD-12-0210 abstract -----	1-21

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2016/053056

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2013144339 A1	03-10-2013	AU 2013241664 A1	02-10-2014
		CA 2866229 A1	03-10-2013
		CN 104321058 A	28-01-2015
		EP 2830626 A1	04-02-2015
		JP 2015511621 A	20-04-2015
		KR 20140145133 A	22-12-2014
		RU 2014143517 A	27-05-2016
		US 2015072019 A1	12-03-2015
		WO 2013144339 A1	03-10-2013
